REMARKS/ARGUMENTS

By this Amendment, the specification is amended, and claims 34 and 36 are amended. Claims 1-4, 6-9, and 12-37 are pending. Support for the amendment to claims 34 and 36 can be found throughout the Specification as filed, and specifically there is support for a range of time in the Specification which states:

> At 1 volt, a current peak was observed during the first 2 seconds of electrification. The current declined sharply over the following 13 seconds. Experiments applying 5 volts gave rise to currents that remained relatively stable over the entire electrification period (15 seconds). [Emphasis Added, ¶[0098]].

Thus the concept of a range of time over which the stimulus can be applied is clearly present in the Specification as filed. In addition, support for this limitation can be found throughout the Specification as filed, specifically ¶[0149] which discloses "[i]mmediately after 3 seconds of electrification", ¶[0145] which discloses "the same samples were subjected to 1 V DC electrification for 4 seconds", ¶[0121] which discloses that "to 5V DC electrification for 11 seconds", and ¶[0114] which discloses "1 V treatment for 15 seconds".

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The Examiner's courtesy in granting an interview to Applicants' representative on May 9, 2006 is gratefully acknowledged. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

Citations to the Specification are based on U.S. Patent Application Publication 2002/0137056 (Erikson et al.).

Objection to the Specification

The Examiner has objected to the Speciation as allegedly incorporating essential subject matter by reference. Applicant respectfully traverses the foregoing objection. Support for the limitation wherein the homologous duplex is substantially free of Hoogsteen bonding and G-G quartets can be found in U.S. Patent No. 6,656,692, (column 5, lines 56-63) incorporated by reference in this Specification, see ¶[0059]. However, solely in an effort to expedite prosecution of the instant application, Applicant has amended the Specification to recite the allegedly essential subject matter, *supra*. Withdrawal of the objection is respectfully requested.

Rejection under 35 USC 112 first paragraph

Claims 34 and 36 stand rejected under 35 USC 112 first paragraph as allegedly failing to comply with the written description requirement, for recitation of the limitation "for 15 seconds or less". This rejection is respectfully traversed. The Examiner argues that there is not support in the Specification for a range of time periods from 0 to 15 seconds. However, the claims as amended recite that the time period is from 2 to 15 seconds. Support for this limitation has been set forth, *supra*.

Accordingly, reconsideration and withdrawal of the rejection of claims 34 and 36 under 35 USC 112 first paragraph is respectfully requested.

Rejection under 35 USC 112 second paragraph

Claims 1-4, 6-9, 12-25, and 30-35 stand rejected under 35 US 112 second paragraph as allegedly being indefinite. This rejection is respectfully traversed. The Examiner argues that the claim is drawn to a property of the probe, that is that it hybridizes to the target to form, for

example, a quadruplex, allegedly without reciting a method step. In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph "by providing clear warning to others as to what constitutes infringement of the patent". See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). MPEP 2173.02, MPEP 2173.02. In the instant case, the claim as written contains a method step of adding the probe and the target to form a test solution, and the claim further sets forth that "said probe hybridizes specifically with said target". This clearly sets forth a hybridization step. The claim as written provides clear warning to others as to what constitutes infringement of the patent, because the limitations of the claim requires that the probe and the target form a test solution, and the that the probe hybridizes specifically with the target. Since the claim meets the requirement of providing clear warning to others as to what constitutes infringement of the patent, the rejection may properly be withdrawn.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4, 6-9, 12-25, and 30-35 stand rejected under 35 US 112 second paragraph is respectfully requested.

Rejection under 35 USC 102

Claims 27-29 and 37 stand rejected as allegedly being anticipated by U.S. Patent No. 5,770,369 (Meade et al.).

The claims are drawn to a method for assaying sequence specific hybridization by combining a target and a probe in a binding medium to provide a sample and treating the sample

with a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization, wherein at least one label is an intercalating agent provided in the test sample and is not covalently bound to said probe or to said target, and further wherein when the first and second stimuli are photonic, there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. The instant claims are novel over the disclosure of the '369 patent for the following reasons. In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." In the instant case, not every element of the claims is present in the '369 patent. The instant claims require at least one non-covalently bound label which is an intercalator, and this is not disclosed in the '369 patent. The '369 patent discloses nucleic acids with electron transfer species covalently attached to a terminal base of the nucleic acid ('369 at column 5, lines 35-40). Example 7 of the '369 patent, which the Examiner cites, is directed to methods using a doubly modified oligonucleotide with electron transfer moieties as a photoactive probe for homologous nucleic acid sequence detection ('369 at column 34, lines 7-10), wherein the modified oligonucleotides each have an electron transfer moiety attached (see '369 at column 33, lines 24-34, Example 6). This is in contrast to the instantly claimed method, which contains the limitation requiring at least one non-covalently bound label which is an intercalator. Since this limitation is not disclosed in the '369 patent, the '369 patent does not anticipate the instant

claims.

In addition, the claims have the limitation wherein there is a second stimulus applied and the second signal is measured, and the two signals are compared as a measurement of sequence specific hybridization. The Examiner cites Example 7 of the '369 patent as allegedly disclosing this limitation. However, in Example 7 amplified target DNA is added to a hybridization solution containing 50 nanomoles of doubly labeled 24-mer probe modified oligonucleotides each have an electron transfer moiety attached (see '369 at column 33, lines 24-34, Example 6). Hybridization is allowed to proceed at 60°C for 10 minutes with gentle agitation. Detection of electron transfer following laser excitation is carried out as in Example 5 of the '369 patent. There is only the single excitation and measurement of signal, there is not a second stimulus and not a second signal measurement. Thus, the '369 patent does not disclose a first and a second stimulus, does not disclose measuring the signal from both the first and second stimulus, and also does not disclose comparing the signals. Since these limitations are not disclosed in the '369 patent, the '369 patent does not anticipate the instant claims.

Furthermore, the instant claims recite the limitation wherein when the first and second stimuli are photonic, there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. This limitation is not disclosed in the '369 patent. Since this limitation is not disclosed in the '369 patent, the '369 patent does not anticipate the instant claims.

Accordingly, reconsideration and withdrawal of the rejection of claims 27-29 and 37 under 35 USC 102(b) over U.S. Patent No. 5,770,369 (Meade et al.) is respectfully requested.

Rejections under 35 USC 103

Claims 1-4, 6-9, 12-26, and 30-35 stand rejected under 35 USC 103(a) allegedly being unpatentable over U.S. Patent No. 6,071,699 (Meade et al.) in view of either U.S. Patent No. 6,426,407 (Fresco et al.) or U.S. Patent No. 5,874,213 (Cummins et al.).

The claims are drawn to a method for assaying sequence specific hybridization by combining a target and a probe in a binding medium to provide a sample and treating the sample with a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization, wherein when the first and second stimuli are photonic, there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus, wherein the probe biopolymer sequence and the target biopolymer sequence contain nucleobases and the probe hybridizes specifically with said target to form a homologous duplex, a homologous triplex, a homologous quadruplex, a Watson-Crick triplex or a Watson-Crick quadruplex, and further wherein the method is conducted without separating probe-target complexes from free probes and targets.

The claims are patentable over a combination of the '699 patent and either the '407 or '213 patents for the following reasons. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach

or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP 2143.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

In the instant case, not every element of the claims is taught or suggested by the combination of the '699 patent and either the '407 or '213 patents. The claims have the limitation wherein there is a second stimulus applied, and a second signal is measured, and the first and second signals are compared as a measurement of sequence specific hybridization. The Examiner cites Example 7 of the '699 patent as allegedly disclosing this limitation. However, in Example 7 amplified target DNA is added to a hybridization solution containing 50 nanomoles of doubly labeled 24-mer probe modified oligonucleotides each have an electron transfer moiety attached (see '699 at column 33, lines 50-60, Example 6). Hybridization is allowed to proceed at 60°C for 10 minutes with gentle agitation. Detection of electron transfer following laser excitation is carried out as in Example 5 of the '699 patent. There is only the single excitation and measurement of signal, there is not a second stimulus and second measurement. Thus, the '699 patent does not disclose a second stimulus, further does not disclose measuring the signal from both the first and second stimulus, and also does not disclose comparing the signals. Since

this limitation is not disclosed in the '699 patent, the '699 patent does not disclose or suggest all the limitations of the instant claims.

In addition, the instant claims recite the limitation wherein when the first and second stimuli are photonic, there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. This limitation is not disclosed in the '699 patent. For example, in Example 7 of the '699 patent, there is a stimulus applied top the modified nucleic acids which is photonic (laser excitation, column 33, line 67), but there is no intermediate electronic stimulus applied to the test sample after the first stimulus and before any second stimulus. In fact, there is no second stimulus applied at all. Since this limitation is not taught in the '699 patent, the '699 patent does not disclose or suggest all the limitations of the instant claims. The Examiner alleges that the '699 patent meets this limitation in Table 2 (column 23) which allegedly discloses "light plus electronic" stimulation, and argues that the '699 patent thus discloses both photonic and electronic stimulation as claimed. However, the claims contain the limitation wherein there is a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization. Here, there is no second stimulus disclosed or suggested, and there is no measurement of the second signal disclosed or suggested, and no step comparing the first and second signals is disclosed or suggested by the '699 patent.

Furthermore, the instant claims recite the limitation wherein the probe biopolymer sequence and the target biopolymer sequence contain nucleobases and the probe hybridizes specifically with said target to form a homologous duplex, a homologous triplex, a homologous

quadruplex, a Watson-Crick triplex or a Watson-Crick quadruplex. These forms are not taught or suggested in the '699 patent, as the Examiner admits on page 6 of the Office Action. The '699 patent does not disclose or suggest all of the limitations of the claims.

All these deficiencies in the '699 patent are not cured by either the '407 or '213 patents. The deficiencies in the '699 patent are not cured by a combination with the '407 patent because the '407 patent discloses synthetic nucleic acid monomers ("residues"), that when incorporated into an oligonucleotide ("third strand"), or analog oligomer, i.e., a third strand with a synthetic backbone, enables the third strand to form a triple-stranded nucleic acid ("triplex") when hybridized to a double-stranded nucleic acid ("duplex"), wherein the "target region" to which the third strand binds is of substantially any base sequence (column 3, line 64 to column 4, line 8). However, the '407 patent does not disclose or suggest a method wherein there is a second stimulus applied and the second signal is measured, and the two signals are compared as a measurement of sequence specific hybridization. Additionally, the '407 patent does not disclose or suggest a method wherein there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. Furthermore the '407 patent does not disclose or suggest a method wherein there is a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization. Since neither the '699 nor the '407 patent disclose or suggest these limitations, the combination of the patents does not disclose or suggest these limitations.

Furthermore, there is no motivation for one of skill in the art to alter the methods of the

'699 patent or '407 patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the '407 patents to alter the method disclosed in the '699 patent to arrive at the instantly claimed method. The Examiner argues that the motivation is the expected benefit of improved binding control useful in the isolation and identification of diagnostic and research applications as taught in the '407 patent. However, the combination of the '699 patent and the '407 patent does not disclose or suggest methods wherein there is a second stimulus applied, the second signal is measured, and does not disclose or suggest methods wherein the two signals are compared as a measurement of sequence specific hybridization or a method wherein there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. Since the combination of the patents does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Furthermore, all the deficiencies in the '699 patent are not cured by a combination with the '213 patent because the '213 patent discloses capillary electrophoretic techniques to the isolation and separation of oligonucleotides containing specific desired nucleobase sequences, and quantitative capillary electrophoretic techniques for such isolations. However, the instant claims have the limitation wherein the method is conducted without separating probe-target complexes from free probes and targets. However, the '213 patent is directed to capillary gel electrophoresis, a method which will separate bound probe-target complexes from free probes and free targets, which is contrary to the instantly claimed method. In addition, the '213 patent does not disclose or suggest a method wherein there is a second stimulus applied and the second

signal is measured, and the two signals are compared as a measurement of sequence specific hybridization. Additionally, the '213 patent does not disclose or suggest a method wherein there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. Furthermore, the '213 patent does not disclose or suggest a method wherein there is a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization. Since neither the '699 nor the '213 patent disclose or suggest these limitations, the combination of the patents does not disclose or suggest these limitations.

Additionally, there is no motivation for one of skill in the art to alter the method of the '699 patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the '213 patents to alter the method disclosed in the '699 patent to arrive at the instantly claimed method. The Examiner argues that the motivation is the alleged expected benefit of improved detection of the complexed target as disclosed in the '213 patent. However, the '213 patent is directed to methods using capillary gel electrophoresis, while the instant claims contain the limitation that free probes and primers are not to be separated from bound probes and primers. The practice of the method of the '213 patent depends on the separation of free probes and primers from complexed probes and primers. Accordingly, there is no motivation to arrive at the instant claims given the combination of the '699 and '213 patents, and no expectation of success since the combination of the '699 and '213 patents would require a method wherein the free probes and primers are separated from complexed probe and primers.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4, 6-9, 12-26,

and 30-35 under 35 USC 103(a) allegedly being unpatentable over U.S. Patent No. 6,071,699 (Meade et al.) in view of either U.S. Patent No. 6,426,407 (Fresco et al.) or U.S. Patent No. 5,874,213 (Cummins et al.) is respectfully requested.

Claim 36 stands rejected under 35 USC 103(a) as allegedly being obvious over U.S. Patent No. 6,071,699 (Meade et al.).

The claim is drawn to a method for assaying sequence specific hybridization by combining a target and a probe in a binding medium to provide a sample and treating the sample with a first stimulus, measuring a first signal, applying a second stimulus and measuring a second signal, and comparing the two signals as a measurement of sequence specific hybridization, wherein there is an intermediate electronic stimulus applied after the first stimulus and before the second stimulus, wherein the intermediate stimulus is applied to the test sample for 2 to 15 seconds.

The claim is patentable over the '699 patent for the following reasons. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP 2143.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

In the instant case, not every element of the claim is taught or suggested by the '699 patent. Claim 27 from which claim 36 depends requires at least one non-covalently bound label which is an intercalator, and this is not taught or suggested in the '699 patent. The '699 patent discloses nucleic acids with electron transfer species covalently attached to a terminal base of the nucleic acid ('699 at column 5, lines 35-40). Example 7 of the '699 patent, which the Examiner cites, is directed to methods using a doubly modified oligonucleotide with electron transfer moieties as a photoactive probe for homologous nucleic acid sequence detection (column 34, lines 7-10), wherein the modified oligonucleotides each have an electron transfer moiety attached ('699 at column 33, lines 24-34, Example 6). This is in contrast to the instantly claimed method, which contains the limitation requiring at least one non-covalently bound label which is an intercalator. Since this limitation is not taught in the '699 patent, the '699 patent does not teach or suggest all the limitations of the instant claims.

In addition, claim 27 from which claim 36 depends recites the limitation wherein there is a second stimulus applied and the second signal is measured, and the two signals are compared as a measurement of sequence specific hybridization. The Examiner cites Example 7 of the '369 patent as allegedly disclosing this limitation. However, in Example 7 amplified target DNA is

added to a hybridization solution containing 50 nanomoles of doubly labeled 24-mer probe modified oligonucleotides each have an electron transfer moiety attached ('699 at column 33, lines 24-34, Example 6). Hybridization is allowed to proceed at 60°C for 10 minutes with gentle agitation. Detection of electron transfer following laser excitation is carried out as in example 5. There is only the single excitation and measurement of signal, there is not a second stimulus and second measurement. Thus, the '699 patent does not disclose or suggest a first and a second stimulus, does not disclose or suggest measuring the signal from both the first and second stimulus, and does not disclose or suggest comparing the signals. Since this limitation is not taught or suggested in the '699 patent, the '699 patent does not render the instant claim unpatentable.

In addition, claim 27 from which claim 36 depends recites the limitation wherein when the first and second stimuli are photonic, there is an intermediate electronic stimulus applied to the test sample after the first stimulus and before the second stimulus. This limitation is not disclosed in the '369 patent. Since this limitation is not taught in the '699 patent, the '699 patent does not anticipate the instant claims.

Furthermore, the '699 patent does not disclose or suggest a method wherein the intermediate stimulus is applied to the test sample for 2 to 15 seconds. The Examiner alleged that the '669 patent discloses that voltage is applied and detected using pulse methods, and alleges that the patent disclose optimization of the pulse based on the sample. The Examiner argues that it would have been obvious to one of ordinary skill in the art to derive the optimal pulse time based on the suggestion in the '699 patent to do so. However, the '699 patent

discloses optimization of the voltage not of the time of the pulse:

> The device for measuring electron transfer amperometrically involves sensitive (nanoamp to picoamp) current detection and includes a means of controlling the voltage potential, usually a potentiostat. This **voltage is optimized** with reference to the potential of the electron donating complex on the nucleic acid. ['699 at column 27, lines 21-23, Emphasis Added].

Thus, there is no teaching or suggestion in the '699 patent regarding any alleged optimization of the time period of a pulse application. Thus, the '699 patent does not disclose or suggest a method wherein the intermediate stimulus is applied to the test sample for 2 to 15 seconds.

Accordingly, reconsideration and withdrawal of the rejection of claim 36 under 35 USC 103(a) allegedly being unpatentable over U.S. Patent No. 6,071,699 (Meade et al.) is respectfully requested.

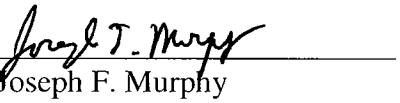
For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

August 15, 2006

By 
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